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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,792	08/16/2007	Maria Luz Lopez-Rodriguez	6102-000031/NP	5328

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EXAMINER	
BIANCHI, KRISTIN A	

ART UNIT	PAPER NUMBER
1626	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,792	LOPEZ-RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	KRISTIN BIANCHI	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/13/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-41 are pending in the instant application. Claims 1-41 are rejected.

Information Disclosure Statement

The information disclosure statement filed on July 13, 2007 was considered and a signed copy of form 1449 is enclosed herewith.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Spain on January 30, 2005. It is noted, however, that applicant has not filed a certified copy of the P 200400205 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC §§ 101 & 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claims 21-23 are drawn to *the use* of compounds of the formula I, but since the claims do not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 21-23 are rejected under 35 U.S.C. § 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131,149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 and 24-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claims 1 and 24 recite that X is selected from the group consisting of C2-C10-alkylene, **C2-C10-alkenylyne**, and –CH2-Y-CH2-. It is unclear what Applicant intends "C2-C10-alkenylyne" to mean since it is undefined in the specification and this makes the claims indefinite. In the remarks filed (July 31, 2006) with the preliminary amendment, Applicant states "Claim 1 has been amended to replace 'C2-C10-alkyl' and 'C2-C10-alkenyl' in the X definition with 'C2-C10-alkylene' and **'C2-C10-alkenylene'**, respectively." "C2-C10-alkenylyne" was given the definition of C2-C10-alkenylene (i.e. any of a series of divalent radicals of the general formula C_nH_{2n} derived from aliphatic hydrocarbons with at least one double bond) for the sake of this office action. "C2-C10-alkenylyne" is taken to mean that there is at least one triple bond in the chain and it appears as though Applicant does not intend for this to be the definition since there are

no examples present in the specification with this type of chain. It appears as though "C2-C10-alkenylyne" is a typo. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20 and 24-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I, stereochemical isomers and pharmaceutically acceptable salts thereof, does not reasonably provide enablement for hydrates or solvates thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The state of the prior art/level of ordinary skill/level of predictability

Active pharmaceutical ingredients are frequently delivered to the patient in the solid-state as part of an approved dosage form (e.g., tablets, capsules, etc.). Solids provide a convenient, compact, and generally stable format to store an active

pharmaceutical ingredient or a drug product. Understanding and controlling the solid-state chemistry of active pharmaceutical ingredients, both as pure drug substances and in formulated products, is therefore an important aspect of the drug development process. Active pharmaceutical ingredients can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals, and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability, and other performance characteristics of the drug. Hence, it is critical to understand the relationship between the particular solid form of a compound and its functional properties.

For ionizable compounds, preparation of salt forms using pharmaceutically acceptable acids and bases is a common strategy to improve bioavailability. However, the preparation of other solid forms, such as solvates and hydrates, are not so common to be predictable. In order to obtain patent protection on these forms, some of which may have significantly different properties and relevance as development candidates, it is essential to prepare them, identify conditions for making them, and evaluate their properties as valuable new pharmaceutical materials.

Therefore, for the reasons above, the state of the prior art is one of unpredictability.

As stated above, crystalline solids can exist in the form of polymorph, solvates or hydrates. "Phase transitions such as polymorph interconversion, desolvation of solvate, formation of hydrate, and conversion of crystalline to amorphous form may occur during various pharmaceutical processes, which may alter the dissolution rate and transport

characteristics of the drug. Hence, it is desirable to choose the most suitable and stable form of the drug in the initial stages of drug development" (Vippagunta et al., abstract). In further discussing the predictability of the formation of solvates, Vippagunta et al. discloses that "predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds" (page 18, section 3.4).

The amount of direction or guidance present/existence of working examples

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds which fall within the scope of a claim will posses the alleged activity. The specification does not adequately enable a method of making the solvates or hydrates of the compounds that the claims encompass.

There is no data present or any working examples in the specification for the preparation of solvates or hydrates of said compounds.

The quantity of experimentation needed

While the level of skill in the pharmaceutical arts is high, it would require undue experimentation for one of ordinary skill in the pertinent art to prepare any solvate or hydrate of said compounds.

The specification provides limited support, as noted above, for the solvates or hydrates encompassed by the claims. The quantity of experimentation needed to make

the solvates or hydrates encompassed by the claims would be an undue burden on one skilled in the chemical art, since the skilled artisan is given inadequate guidance for the reasons stated above. Also, the science of crystallization has evolved such that, without guidance or working examples in the specification, the claim lacks enablement.

This discussion established *prima facie* non-enablement. Deletion of the words "solvate" and "hydrate" from the claims would overcome this rejection.

Claims 24-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cerebral damage caused by thromboembolitic stroke or traumatic brain damage, depression, psychosis, and mood disorder, does not reasonably provide enablement for a method of preventing any of the conditions listed above or for the treatment or prevention of Parkinson's disease, migraine, pain, and urinary tract disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The state of the prior art and the predictability or lack thereof in the art

The term "preventing" actually means to anticipate or counter in advance, to keep from happening, etc. and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "preventative" effect.

The state of the prior art is that the pharmacological art involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can prevent or treat which specific diseases by what

mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instantly claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic and preventive effects of the above listed conditions, whether or not the condition is affected by the 5-HT1A receptor would make a difference.

Applicants are claiming methods which include the prevention and/or treatment of various diseases such as Parkinson's disease, migraine, pain, urinary tract disorder, etc.

In regards to the prevention and/or treatment of pain, enablement for the scope of treating pain generally is not present. There is a vast range of forms that in can take, causes for the problem, and biochemical pathways that mediate the pain reaction. There is no common mechanism by which all, or even most, pain reactions arise. It is not reasonable to accept any agent to be able to treat pain generally.

In regards to the prevention and/or treatment of Parkinson's disease, migraine, pain, and urinary tract disorder, it does not appear that 5-HT1A receptor plays an important role in the prevention and/or treatment of these conditions (i.e. see Nichols et al., pages 1630 and 1631, section 2.3.1) and according to the specification (i.e. page 41) "most of the compounds are highly selective for the 5-HT1A receptor" over the other receptors.

Hence, in the absence of a showing of correlation between all the conditions claimed as capable of treatment or prevention with modulation of the 5-HT1A receptor, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims due to the unpredictability.

The amount of direction or guidance present and the presence or absence of working examples

The only direction or guidance present in the instant specification is the *in vitro* binding assays for the different receptors and the *in vitro* and *in vivo* neuroprotection studies.

The uses covered by the claims are not enabled based solely on the assay testing reported in the specification. Various studies reported for compounds in clinical development rely on animal models and not simply assay testing as done herein. Note Hoffman V. Klaus 9 USPQ2d 1657 regarding the standard of testing that is necessary to establish the likelihood of *in vivo* use. Also see Ex parte Powers 220 USPQ 925. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of *in vivo* efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte

Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of *in vivo* success for any additional diseases that may still be embraced in response to this action. See MPEP 2164.05(a).

Further, there is no disclosure regarding how all types of conditions claimed having divers mechanisms are treated or prevented. Receptor activity is generally unpredictable and a highly structure specific area, and the data provided of is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat or prevent the extremely difficult diseases embraced by the instant claims.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds except for the *in vivo* neuroprotection study (i.e. pages 45 and 46). Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved." See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what diseases out of the multitude claimed would be benefited (treated or prevented) by the administration of the compound of formula I.

The level of skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which conditions would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of the various claimed diseases and disorders as a result necessitating one of skill to perform an exhaustive search for which disorders can be treated or prevented by what compounds of the instant claims in order to practice the claimed invention.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instantly claimed methods. In view of the chemical nature of the invention and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that" a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable". Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art

would have to engage in undue experimentation to test which diseases can be treated or prevented by the compound encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

At least claims 1, 19, 20 and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2004/014915. WO 2004/014915 disclosed the same subject matter as US Patent No. 7,351,732 and since WO 2004/014915 is in Spanish, the disclosure of US Patent No. 7,351,732 will be used for this rejection.

Specifically, claim 7 of US Patent No. 7,351,732 lists (column 24, lines 43 and 44) the compound 2-[4-[2-(o-Methyoxyphenyl)ethylamine]butyl]-1,3-dioxoperhydropyrrolo[1,2-c]-imidazol, for example, and this anticipates a compound of formula I of the instant claims (i.e. this compound is listed in claim 19 of the instant claims as [[(m)]]). US Patent No. 7,351,732 also discloses that the compounds of Formula I are used for the treatment of a pathological state (i.e. claim 17), which can include the conditions listed in claim 24 of the instant claims, and for the treatment of cerebral damage produced by thromboembolic stroke or cranium brain traumatic injuries (i.e. claim 19).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

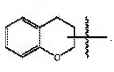
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 and 24-41 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 6-8, 13-19, and 21-23 of U.S. Patent No. 7,351,732. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons given below.

U.S. Patent No. 7,351,732 discloses compounds of the Formula I (i.e. claim 1)

which anticipate compounds of the instant claims wherein R5 is



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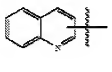

. U.S. Patent No. 7,351,732 also discloses using

these compounds for the treatment of a pathological state and to provide neuroprotection. Since there is significant overlapping subject matter in the current application and U.S. Patent No. 7,351,732, it would have been obvious to one of ordinary skill in the art to make the compounds of the instant claims given U.S. Patent No. 7,351,732 and to use them for the treatment of the conditions listed in claim 24, such as cerebral damage caused by thromboembolitic stroke or traumatic brain damage.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KRISTIN BIANCHI whose telephone number is (571)270-5232. The examiner can normally be reached on Mon-Fri 7am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kamal A Saeed/
Primary Examiner, Art Unit 1626

Kristin Bianchi
Examiner
Art Unit 1626

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